SUBACUTE SCLEROSING LEUKOENCEPHALITIS*

Clinical and Ultrastructural Studies

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Dawson,[1] in 1933, described a rapidly progressive fatal disease of children and young adults characterized clinically by dementia, seizures, extrapyramidal signs, spasticity and, pathologically, by subacute inflammatory changes and intranuclear inclusions in neurons and glial cells. In 1945, van Bogaert[2] defined a similar condition but without prominent intranuclear inclusions and called it subacute sclerosing leukoencephalitis (SSLE). It is now generally felt that these represent variations of the same disease.[3]

The etiology of this condition has never been proved, although the subacute inflammatory changes and the presence of Cowdry type A intranuclear inclusions suggest a viral etiology. As further evidence for

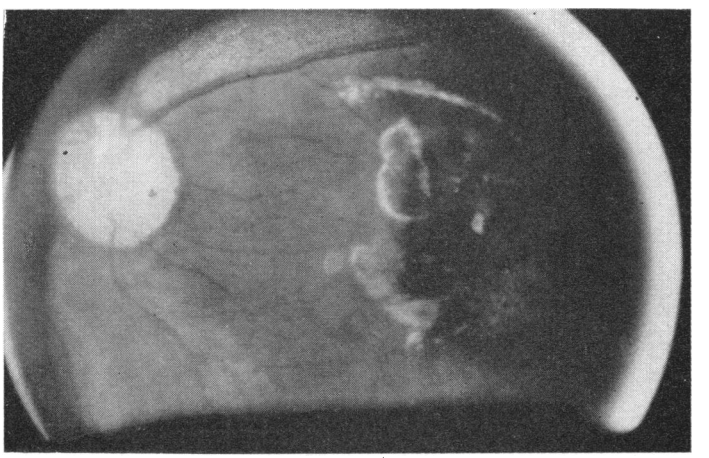

Fig. 1. Right eye. Large area of sharply demarcated chorioretinitis involving macular region. Pale optic disc.

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this hypothesis, successful animal passage of a pathogenetic factor has been carried out.[4, 5]

Still further proof of a viral etiology has come from two laboratories in France[6, 7] where filamentous intranuclear inclusions resembling viral components have been observed under the electron microscope, and from this country[8, 9] where spherical particles resembling fully formed viruses have been seen.

One of the coauthors (Isabel Tellez-Nagel) has previously documented both of these findings in ultrastructural studies performed on a cerebral biopsy from a patient with SSLE.[10] The clinical details of this case have not been published previously and these findings have recently been further elaborated by means of tissue obtained at autopsy.

Case Report

A seven-year-old Negro boy was admitted to the Bronx Municipal Hospital Center on November 8, 1965, following one month of precipitous deterioration of his school work and progressive inattention and lethargy. During the three days prior to admission he developed stiffening and posturing of his right and then left hand, his speech became very slow, and he began to perseverate.

In retrospect it became evident that a behavior problem with some hyperactivity had begun eight months previously. Family history and past medical history were noncontributory.

Examination. General physical examination was normal. The child was confused and disoriented. Large gaps in memory were present, and he attempted to cover up for these with stereotyped vocal mannerisms and perseveration. He could not read or write, and he experienced some difficulty in finding words.

Examination of the fundi showed large areas of grey pigmentation in the macular regions of both eyes (Figure 1). The right optic disc was pale, and the left normal. Visual acuity and visual fields could not be tested. The remainder of the cranial nerve examination was normal.

The boy moved very slowly and *en bloc*. Sitting balance was poor and there was titubation of the head and trunk. There was dystonic posturing of the hands and cogwheel rigidity in all extremities, but no resting tremor. Movements of the hands and fingers were slow and clumsy. A mild intention tremor was present.

Gait was slow, with widened base and festination. The patient

could not walk on his heels or toes. Deep tendon reflexes were symmetrical and brisk. Plantar responses were flexor. No sensory abnormalities could be detected.

Laboratory. Blood count, urinalysis, electrolytes, liver function tests, and serology were normal. Cerebrospinal fluid was clear and contained three lymphocytes. Total protein was 29 mg. per cent with 35.9 per cent gamma globulin (serum protein 9.1 gm. per cent with 24.7 per cent gamma globulin).

X-ray films of the skull and chest were normal. Electromyography revealed fibrillations in the right anterior tibial muscle.

Electroencephalogram initially showed paroxsymal bursts of 2-4 cps slow waves, without clear periodicity, and arising from a mildly slow background. Three weeks later, periodic bursts of 1½ cps activity occurred, with an interval of about six seconds between bursts. The final record, 1½ weeks after the second, showed similar periodic activity at intervals of eight seconds and relative flattening of background activity between these bursts.

Course. Rigidity and dystonic posturing increased in severity and the patient lost all ability to carry out voluntary movements. Meaningful contact with the environment ceased. Deep tendon reflexes became hyperactive and bilateral Babinski signs appeared. The chorioretinitis increased in extent. Myoclonic jerks began shortly after admission, increased rapidly in frequency, then gradually disappeared. Frequency was not decreased during a trial of diazepam.

Pseudobulbar involvement of the pharyngeal musculature led to aspiration pneumonitis, and necessitated tracheostomy and nasogastric feeding.

A cerebral biopsy was performed without incident one month before death. The patient died 2½ months after admission to the hospital.

Methods

In addition to routine histologic examination of fresh formalin-fixed tissue, tissue from both biopsy and autopsy specimens was fixed in osmium tetroxide, dehydrated in a graded series of ethanols, and embedded in Araldite. Thin sections were cut on a Porter-Blum microtome, mounted on bare copper grids, and stained with lead acetate and uranyl acetate. Examination was carried out in a Hitachi HS7 electron microscope.

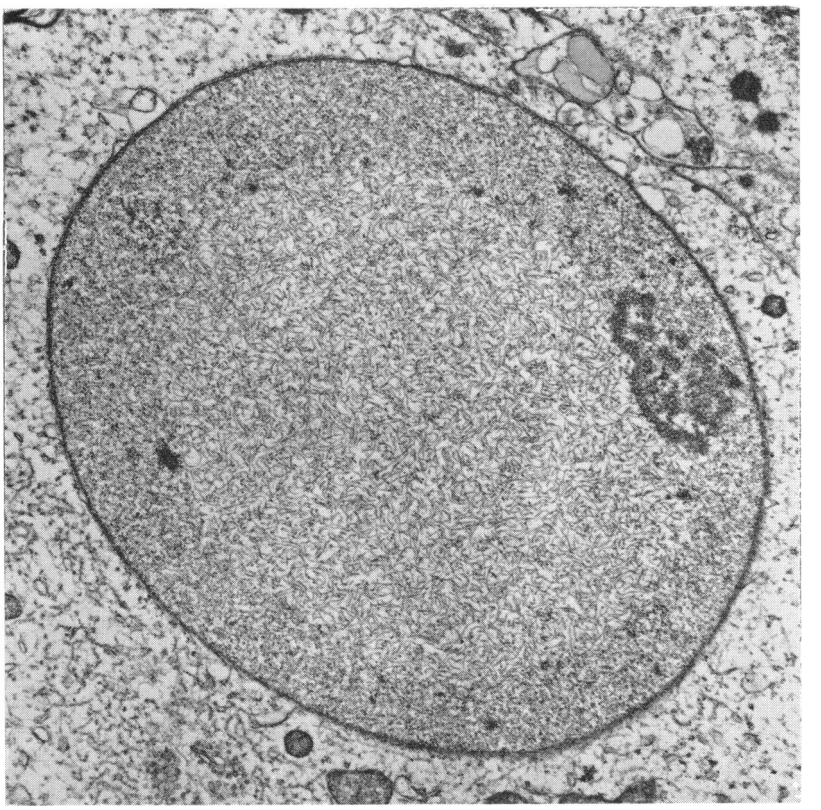

Fig. 2. Nucleus of glial cell, filled with a mass of tubular elements. ×14,500.

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Histological Examination

Gross examination of the brain at autopsy showed the healed surgical wound at the site of the previous biopsy in the right frontal region. There was diffusely increased firmness of the white matter. Mild atrophy of the cerebellar folia was present.

The hematoxylin-eosin preparation showed the presence of severe cortical damage with marked loss of neurons. Many remaining neurons revealed swelling and pyknosis of their nuclei and hyalinization of cytoplasm. There was a great increase in microglia, and many reactive astrocytes were present. Numerous eosinophilic intranuclear and intracytoplasmic inclusions were present in neurons, but only intranuclear inclusions were found in glial cells.

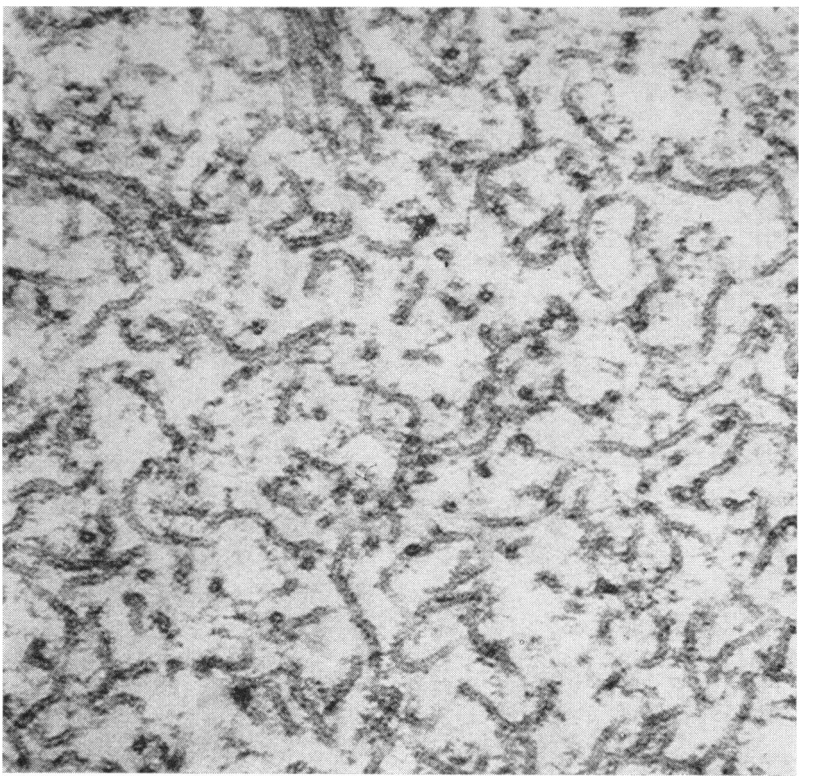

Fig. 3. Higher resolution, demonstrating tubular nature of filaments and circular cross-section. ×22,000.

There was diffuse pallor of myelin and some areas of spongy change in the white matter. Reactive astrocytes and fat-laden macrophages were prominent. Many glial cells contained eosinophilic intranuclear inclusions.

A dense leptomeningeal and perivascular infiltrate of lymphocytes and plasma cells was seen. A few eosinophiles, polymorphonuclear leukocytes, and macrophages were also present. Although all of these changes were diffuse throughout the brain, the most severe change was present in the temporal and frontal regions and the basal ganglia.

Electron Microscopy

The intranuclear inclusions in glial cells were found to consist of a mass of interwoven filamentous structures that virtually filled the nucleus (Figure 2). A tubular structure was suggested by the dark-

light-dark sequential pattern on longitudinal section and was confirmed by a circular configuration on cross-section (Figure 3). The diameter of each filament was 170-230Å., and the length at least 4000 Å. This is a minimal estimate of length, as the filaments are somewhat wavy and move in and out of the plane of section. In some places, transverse striations are seen with a periodicity of 115 Å.

Many of the cells that contained intranuclear filaments also contained cytoplasmic inclusions consisting of dense, granular, coarsely filamentous masses, which lacked the definition and regular appearance of the intranuclear tubules.

Another finding was the presence of particles that bore a resemblance to fully formed viruses lying free in the cytoplasm of many cells (Figure 4). These were observed only in cells that did not also contain intranuclear filaments. These particles were circular, had a diameter of 600-800 Å., and consisted of a dense central core surrounded by a clear halo and then a membrane. In some cases, the core was less dense, and the over-all appearance of a double ring was seen. This difference may be a function of the plane of section. In still other instances the structure seemed to be that of a double core in a single shell.

Comment

The clinical features of the case presented are typical of SSLE. In general, the course may be divided into three stages.[11] Initially there are only personality changes and early evidence of progressive intellectual deterioration. Extrapyramidal signs and seizures, either generalized or more typically myoclonic, follow. Finally the patient develops total dementia and generalized spasticity or rigidity, and death follows.

Retinal changes have been described by several authors. Chao[12] mentions papilledema, retinitis, optic atrophy, and choroidal or macular pigmentation. In Chao's own series of 40 cases of SSLE, two patients showed abnormalities of the ocular fundus; one had bilateral papilledema, and the other had bilateral macular pigmentation and suggestive optic atrophy. Foley and Williams[11] present two patients with papilledema and one with mild optic atrophy. Malamud *et al.*[13] describe a patient with optic atrophy in one eye and macular degeneration and retinal pigmentation in both eyes.

The changes of chorioretinitis in the patient's macular regions bilaterally (Figure 1) were definitely progressive. Unfortunately, his

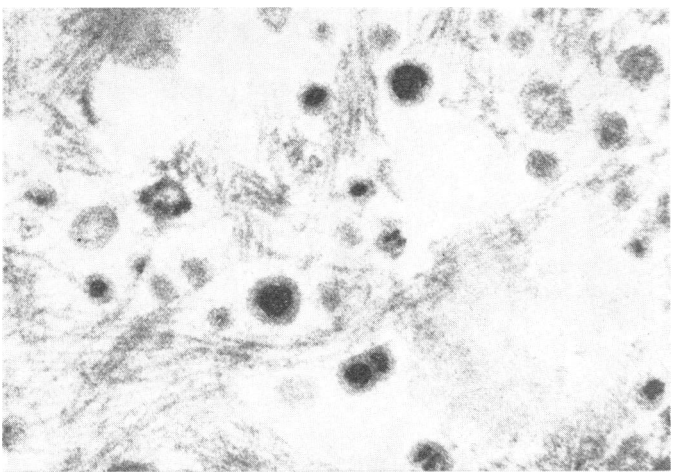

Fig. 4. Spherical particles, illustrating some with solid cores, some with "hollow" cores, and one with two cores within a single shell. ×68,000.

mental condition precluded quantitative testing of vision.

Electroencephalography often provides diagnostic assistance in SSLE. Wave forms and complexes vary somewhat from case to case, but typically show, at some stage of the disease, periodically recurring bursts of high-voltage slow-wave activity. Cobb[14] has demonstrated a one-to-one relation between these bursts and the myoclonic jerks in cases in which both phenomena were present in the same patient.

The increased concentration of gamma globulin in the cerebrospinal fluid of this patient is also typical of SSLE.[15, 16, 17] These findings should be considered characteristic but not specific. The origin of these proteins has not been determined.

The intranuclear tubules that have been demonstrated under the electron microscope in glial cells are identical to those reported in cases of SSLE by Bouteille *et al.*,[6] Perier and Vanderhaegen,[7] and by Nagel and Harter.[9, 18] These authors all feel that these structures represent proof of a viral infection. In comparing these ultrastructural findings with those found in proved viral infections, a close resemblance is seen to the filaments described by Tawara[19] in canine kidney cells infected with measles virus. The tubules in the latter are somewhat smaller, having a diameter of 150-200Å., as compared with 170-230 Å. for SSLE.

The filaments also bear a close resemblance to those found in tissue culture cells infected with the simian parainfluenza virus SV5. Compans

et al.[20] presented electron micrographs that demonstrated that these structures represent the helical nucleocapsid portion of the virus. It seems reasonable to conclude on morphologic grounds that the nuclear inclusions in SSLE represent at least a part of the structure of a virus.

The spherical particles lying free in the cytoplasm of many glial cells are quite similar to those reported by Gonatas and Shy,[8] Gonatas,[9] and Nagel and Harter,[10, 18] The first authors note the similarity of these structures to the fully formed viruses of the Arbo, Polyoma, and Papilloma groups. As an alternative formulation, however, the spheres also resemble those seen in regenerating hepatocytes, and may represent only a reaction of the endoplasmic reticulum.

The final group of data suggesting a viral etiology comes from animal passage experiments. Martin and his co-workers[4] made four consecutive passages of a pathogenetic factor from the brain of a patient with SSLE in mice before losing activity. Pelc *et al.*[5] lost pathogenetic activity after the second passage in monkeys.

Brain tissue from our patient was inoculated into several species of primates by Dr. D. C. Gajdusek's laboratory, but no pathogenetic activity has yet been obtained. This approach is being taken in an attempt to recover a slow virus, as this type of infection has been associated with several progressive neurologic conditions.[21]

Summary

A case of subacute sclerosing leukoencephalitis in a seven-year-old boy has been presented. The clinical, electroencephalographic, and cerebrospinal fluid findings were typical. Diagnosis was subsequently confirmed by cerebral biopsy and postmortem examination.

Electron microscopic examination of brain tissue revealed three abnormalities. There were intranuclear tubular filaments 170-240 Å. in diameter and greater than 4000 Å. in length in the nuclei of glial cells. In addition, cytoplasmic filaments and spherical particles with a diameter of 600-800 Å. were visualized. These findings are strongly suggestive of a viral etiology.

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